Response to Rejection under 35 U.S.C. §102(b)

In the June 26, 2008 Final Office Action, the Examiner rejected claims 90 and 91 under 35 U.S.C. §102(b) as allegedly anticipated by the Physicians' Desk Reference (PDR: 1985) pages 1811-13; Griffith et al. I (Griffith et al., Ann. Surg. 196(9/82):324-329) or Griffith et al. II (Griffith et al., J. Thorac. Cardiovasc. Surg. 99(12/84):952-957) as evidenced by Holschermann et al., Circulation 96(12/97):4232-4238. The Examiner alleged that the pending claims are inherently anticipated by the prior art.

Applicants respectively traverse. The cited references show that CsA may prevent the induction of NF-κB and consequent gene expression, but provide no showing that CsA may reduce gene expression which has been induced. Indeed, the reference cited by the Examiner to explain all the other references, the Holschermann et al. reference, explicitly states that CsA "prevented" NF-κB activation. The Holschermann et al. reference is discussed in detail in Section B herein.

A. The Cited Prior Art

i. 1985 PDR Does Not Teach CsA Administration to Reduce Expression of a Gene that Has Been Induced

On page 3 of the June 26, 2008 Final Office Action, the Examiner alleged that the 1985 PDR "teaches administering the NF-κB inhibitor CsA to patients both prior to **and subsequent** to the transplant, thus rendering moot applicants' and declarant's argument that the reference does not teach prior activation (by surgical procedure or by any of the normal ongoing biochemical influences activating NF-κB) in a human cell of a gene, the expression of which has been induced by an external influence that activates NF-κB" (emphasis original).

In this matter, the applicants respectfully traverse.

The 1985 PDR teaches starting CsA treatment before transplantation and continuing the said treatment post-operation. Specifically, the 1985 PDR provides that "[t]he initial dose of Sandimmune (cyclosporine) Oral Solution should be given 4-12 hours prior to transplantation . . . . The daily dose is continued postoperatively for one or two weeks . . ." (emphasis added, page 1813, first column). Therefore, post-surgery administration of CsA, as disclosed in this reference, merely continues the immunosuppressive therapy that first started before transplantation. Hence, the 1985 PDR teaches only administration of CsA as part of a continuous therapy.

Since the 1985 PDR does not disclose any other external influence that would have necessarily induced NF-κB activity, NF-κB in cells are in an uninduced state prior to administration of CsA. Assuming *arguendo* that transplantation could induce NF-κB activity in cells as alleged by the Examiner, the 1985 PDR teaches preventing such induction by administering CsA *before* the surgery.

In contrast, as discussed in paragraph 6 of the Declaration of Dr. Inder Verma, the pending claims require reducing expression of a gene which has been induced. Claims 90 and 91 recite "reducing expression in a human cell of a gene, the expression of which has been induced" by an extracellular influence that activates NF-κB. Because the 1985 PDR teaches only continuously administering CsA starting before surgery, *i.e.* to prevent induction from occurring in the first place, the 1985 PDR cannot anticipate reducing expression of a gene which has been induced.

In fact there is no evidence of record which even remotely suggests that CsA can reduce gene expression which has been induced. To the contrary, Holschermann et al., which the Examiner alleged explaining the 1985 PDR, in its Figure 1

shows that when transplant surgery is performed without pretreatment with CsA and CsA is administered after the surgery, *i.e.* after the TF gene expression has been induced, cells from the transplant patient have TF gene expression. Thus, not only is the record devoid of evidence that CsA can reduce induced gene expression, Holschermann et al. provides evidence in Figure 1 suggesting CsA cannot reduce gene expression which has been induced.

ii. Griffith et al. I Does Not Teach CsA Administration to Reduce Expression of a Gene that Has Been Induced

On page 3 of the June 28, 2008 Final Office Action, the Examiner alleged that Griffith et al. I "clearly teaches administration of CsA subsequent to the transplant . . . ."

In this matter, the applicants respectively traverse.

Griffith et al. I teaches starting CsA treatment before transplantation and continuing the said treatment post-operation. Specifically, while the section cited by the Examiner for this purpose states that "[f]ollowing cardiac transplantation, immunosuppression is effective with C[s]A . . . ," (Griffith 1981 at 328), the reference also clearly explains that "[c]yclosporin A has been given orally just before operation." (Emphasis added, *Id.* at 324). Therefore, post-operative administration of CsA, as disclosed in Griffith et al. I, merely continues the immunosuppressive therapy that first starts before surgery. Hence, similar to the 1985 PDR, Griffith et al. I teaches only administration of CsA as part of a continuous therapy.

Since Griffith et al. I does not disclose any other external influence that would have necessarily induced NF-κB activity, NF-κB in cells are in an uninduced state prior to administration of CsA. Assuming *arguendo* that transplantation could induce NF-κB activity in cells as alleged by the

Examiner, Griffith et al. I teaches preventing such induction by administering CsA *before* the surgery.

In contrast, as discussed in paragraph 6 of the Declaration of Dr. Inder Verma, the pending claims require reducing expression of a gene which has been induced. Claims 90 and 91 recite "reducing expression in a human cell of a gene, the expression of which has been induced" by an extracellular influence that activates NF-κB. Because Griffith et al. I teaches only continuously administering CsA starting before surgery, *i.e.* to prevent induction from occurring in the first place, Griffith et al. I cannot anticipate reducing expression of a gene which has been induced.

In fact there is no evidence of record which even remotely suggests that CsA can reduce gene expression which has been induced. To the contrary, Holschermann et al., which the Examiner alleged explaining Griffith et al. I, in its Figure 1 shows that when transplant surgery is performed without pretreatment with CsA and CsA is administered after the surgery, *i.e.* after the TF gene expression has been induced, cells from the transplant patient have TF gene expression. Thus, not only is the record devoid of evidence that CsA can reduce induced gene expression, Holschermann et al. provides evidence in Figure 1 suggesting CsA cannot reduce gene expression which has been induced.

iii. Griffith et al. II Does Not Teach CsA Administration to Reduce Expression of a Gene that Has Been Induced

On page 5 of the June 28, 2008 Final Office Action, the Examiner alleged that Griffith et al. II "teaches post-operative administration of CsA to transplant patients and that surgery would be expected to result in expression in a human cell of a gene, the expression of which has been induced by an external influence (surgery and concomitant production of IL-1, TNF, etc.) that activates NF-κB."

In this matter, the applicants respectively traverse.

Griffith et al. II teaches starting CsA treatment before transplantation and continuing the said treatment post-operation. Specifically, Griffith et al. II explains that "[c]yclosporine (10 to 17.5 mg/kg) was given orally 1 to 4 hours preoperatively and continued . . . postoperatively." (Emphasis added, Griffith 1984 at 952). Therefore, post-operative administration of CsA, as disclosed in Griffith et al. II, merely continues the immunosuppressive therapy that first started before transplantation. Hence, similar to the 1985 PDR and Griffith et al. I, Griffith et al. II teaches only administration of CsA as part of a continuous therapy.

Since Griffith et al. II does not disclose any other external influence that would have necessarily induced NF-κB activity, NF-κB in cells are in an uninduced state prior to administration of CsA. Assuming *arguendo* that transplantation could induce NF-κB activity in cells as alleged by the Examiner, Griffith et al. II teaches preventing such induction by administering CsA *before* the surgery.

In contrast, as discussed in paragraph 6 of the Declaration of Dr. Inder Verma, the pending claims require reducing expression of a gene which has been induced. Claims 90 and 91 recite "reducing expression in a human cell of a gene, the expression of which has been induced" by an extracellular influence that activates NF-κB. Because Griffith et al. II teaches only continuously administering CsA starting before surgery, *i.e.* to prevent induction from occurring in the first place, Griffith et al. II cannot anticipate reducing expression of a gene which has been induced.

In fact there is no evidence of record which even remotely suggests that CsA can reduce gene expression which has been induced. To the contrary, Holschermann et al., which the

Examiner alleged explaining Griffith et al. II, in its Figure 1 shows that when transplant surgery is performed without pretreatment with CsA and CsA is administered after the surgery, *i.e.* after the TF gene expression has been induced, cells from the transplant patient have TF gene expression. Thus, not only is the record devoid of evidence that CsA can reduce induced gene expression, Holschermann et al. provides evidence in Figure 1 suggesting CsA cannot reduce gene expression which has been induced.

Summary of the 1985 PDR, Griffith et al. I and II

Contrary to the Examiner's assertion that the 1985 PDR, Griffith et al. I and II disclose that CsA could reduce induced activation of NF-κB, the references consistently teach using CsA to prevent activation of NF-κB. In each case, since CsA was administered before any induction of NF-κB, CsA acts to prevent induction of NF-κB by transplantation. Ensuing post-operative administration of CsA sustains CsA's inhibitory effect to prevent post-operation NF-κB induction. Therefore, since the cited references only teach preventing induction of NF-κB and the pending claims require reducing expression of a gene which has been induced, the 1985 PDR, Griffith I and II do not anticipate the pending claims.

B. The Purported Explanatory Reference - Holschermann et al.

The Examiner alleged that Holschermann et al. can be used to explain what necessarily occurred in the prior art references.

In this matter, the applicants respectively traverse.

As a preliminary matter, Holschermann et al. is not prior art and does not follow the protocols of the prior art, as discussed at length in Applicants' October 19, 2007 response. Holschermann et al. therefore cannot be probative evidence of what occurred in the prior art. Most importantly, Holschermann et al. does not pretreat the transplant patients

with CsA prior to surgery. Notwithstanding the above issues, Holschermann et al. actually supports Applicants' position that CsA cannot reduce expression of a gene which has been induced, as claimed.

Figure 1 does not show any effect of CsA. Figure 1 compares TF activity in cells from transplant patients and from healthy control subjects. Patients were subjected to transplant surgery and were then treated with CsA. (Holschermann 1997 at 4233). Cells were then collected from these patients and from healthy volunteers. Second column shows elevated TF levels, indicating that CsA administration does not reduce TF levels to basal levels. Columns 3 and 4 show increased TF levels due to exposure to the inducer, LPS. Therefore, Figure 1 compares the effect of LPS induction on TF activity in cells from transplant patients and from healthy control subjects, showing both types of cells react to LPS.

On page 7 of the June 26, 2008 Final Office Action, the Examiner asserted that "Table 2 demonstrates that the degree of TF activity generated by mononuclear cells was inversely related to CsA blood levels and was reproducible." More correctly, Table 2 actually shows that CsA, when administered prior to LPS induction, may prevent induction of TF activity.

The legend for Table 2 clearly states that the samples were obtained from transplantation patients "before and 4 hours after CsA administration, respectively, and assayed for TF activity after 6 hours of incubation with LPS . . . ." Therefore, the cells in the column labeled "TF Activity Before CsA Administration" were collected "prior to" CsA administration. On the other hand, the cells in the column labeled "TF Activity After CsA Administration" were collected "following" the CsA administration. After the cells were collected, the cells were exposed to the NF-κB inducer, LPS, to provide the data in Table 2. Thus, the "After CsA Administration" samples have been <u>pretreated</u> with CsA in the

patient before they were collected and before they were exposed to LPS. All samples were subject to LPS challenge for 6 hours before TF activity is measured and recorded in Table 2. The "Before CsA Administration" column shows that LPS stimulation generates TF activity, while the "After CsA Administration" column shows inhibition of LPS-induced TF activity in samples pretreated with CsA prior to challenging with LPS. Therefore, the difference between the "Before" and "After" columns of Table 2 actually shows the preventative effect of CsA pretreatment on TF activity.

The reduction in TF activity observed in the "After" samples, which were pretreated with CsA before being challenged with LPS, cannot support the Examiner's assertion that CsA reduces expression of a gene which has been induced. The Examiner failed to appreciate that the cells in the "After" samples were only subjected to induction by LPS "following" CsA administration. Therefore, any reduction in TF activity is the manifestation of CsA's ability to prevent LPS-induced TF activation.

The Examiner further stated that Figure 2A "show[s] that monocyte TF induction was reduced after CsA application in all transplant recipients" and Figure 2B shows that "9 out of 10 patient samples had decreasing TF activity with increasing CsA administration." Figures 2A and 2B, like Table 2, actually show that when administered prior to induction, CsA may prevent induction of TF activity.

The legend of Figure 2 states that the graphs show TF activity in mononuclear cells (Figure 2A) and purified monocytes/macrophages (Figure 2B) obtained "before and after CsA administration," respectively. Therefore, while the data points labeled as "prior to" consist of cells collected "prior to" CsA administration, the "following" samples have been pretreated with CsA in the patient before they were collected and before they were exposed to LPS. All samples were subject

to stimulation by LPS for 6 hours before TF activity is measured and recorded in Figures 2A and 2B. As shown by negative sloping lines, the "prior to" samples show higher TF activity than corresponding "following" samples, which were pretreated with CsA before stimulation. Therefore, the decrease in TF activity between the "prior to" and "following" samples actually show the effect of CsA pretreatment on TF activity.

The reduction in TF activity observed in the "following" samples, which were pretreated with CsA before being challenged with LPS, cannot support the Examiner's assertion that CsA reduces expression of a gene which has been induced. The Examiner failed to appreciate that the cells in the "following" samples were only subjected to induction by LPS "following" CsA administration. Therefore, any reduction in TF activity is the manifestation of CsA's ability to prevent LPS-induced TF activation.

Furthermore, Applicants respectfully submit that the Examiner misunderstood Figure 3 in Holschermann et al. In fact, Figure 3 confirms that CsA can at best prevent induction of NF-κB. To facilitate this discussion, Applicants enclose an enlarged copy of Figure 3 as **Exhibit A**.

Figure 3 has seven lanes. The first lane shows a molecular marker. All of lanes 2 through 7 consist of cells collected from patients at least 40 days after transplantation. (Holschermann 1997 at 4233). Samples in lanes 2, 3 and 4 were collected in the morning, *i.e.* "prior to" the daily CsA administration, while lanes 5, 6 and 7 consist of samples collected 4 hours "following" the daily CsA administration. *Id.* at 4234. Lanes 2 and 5 show TF mRNA level in peripheral blood mononuclear cells before and after CsA administration. Lanes 3 and 6 also show TF mRNA level before and after the CsA administration, but in purified monocytes/macrophages and lymphocytes, and only after the cells have been incubated for

6 hours without LPS outside the patient. *Id.* at 4234, first paragraph. Lanes 4 and 7 show TF mRNA level after the cells have been challenged, outside the patient, for 6 hours with LPS.

Applicants respectfully submit that Figure 3 fails to provide any evidence that transplantation necessarily induces TF expression. While a faint band corresponding to TF mRNA can be observed in lanes 3 and 6, no corresponding bands are visible in lanes 2 and 5. Importantly, while cells in lanes 2 and 5 are *ex vivo* samples, which are better representation of physiological conditions, the cells in lanes 3 and 6 have been taken out of the patients and subjected to extensive *in vitro* manipulations. As Holschermann et al. described in the Discussion, TF activation may be triggered by many agents, such as "inflammatory cytokines, mitogens, and/or occupancy of cell adhesion molecules." Therefore, the minimal TF mRNA expression observed in lanes 3 and 6 could have been caused by the extensive *in vitro* manipulation of the cells tested in these lanes.

For additional discussion in regard to this matter, Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Inder Verma, submitted in connection with the copending reexamination of U.S. Patent No. 6,410,516, to which the subject application is a continuation of. For the convenience of the Examiner, a copy of the Declaration of Dr. Inder Verma is attached as **Exhibit B**. As discussed in paragraphs 70-72 of the Declaration of Dr. Verma, cells used in this experiment were subject to manipulation and further treatment outside the patients' bodies, which could have induced TF mRNA expression. Therefore, no conclusion can be drawn from lanes 2, 3, 5 and 6 since none of the other cited references describe any *in vitro* manipulation of cells.

Regardless of what lanes 2, 3, 5 and 6 may indicate, lanes 4 and 7 of Figure 3 confirm Applicants' position that CsA at

most may prevent induction of NF-κB. Lanes 4 and 7 show the effect of LPS on TF mRNA expression in cells taken from the patient "prior to" and "following" CsA administration. Specifically, lane 4 consists of cells that were taken out of the patient "prior to" CsA administration. On the other hand, lane 7 consists of cells that were taken out of the patient "following" CsA administration. Thus, the cells of lane 7 have been pretreated with CsA in the patient before they were collected and before they were exposed the inducer LPS. After the cells were taken out of the patients, the cells of both lanes 4 and 7 were subjected to LPS challenge for 6 hours before TF mRNA expression level was measured. Lane 4 shows that LPS does induce TF mRNA expression, by virtue of a much brighter band as compared to lane 3. Lane 7 shows that in cells that were pretreated with CsA before challenging with LPS, such induction is inhibited. Thus, the difference between lanes 4 and 7 actually shows the effect of CsA pretreatment on LPS-induced TF mRNA expression.

The reduction in TF mRNA expression observed in lane 7, which is pretreated with CsA before being challenged with LPS, cannot support the Examiner's assertion that CsA reduces expression of a gene which has been induced. The Examiner failed to appreciate the difference between lanes 4 and 7. Because the cells in lane 7 were subjected to LPS induction "following" CsA administration, whereas the cells in lane 4 were induced without the same CsA pretreatment, any reduction in TF mRNA level is the manifestation of CsA's ability to prevent LPS-induced TF activation.

Thus, Holschermann et al. at best only confirms that CsA may prevent TF expression, and NF-κB activation to the extent such correlation is valid, but does not show that CsA reduces induced activity.[1] This is further supported by Holschermann

[1] Scientific evidence show that CsA exerts its immunosuppressive effects through a different transcription factor called NFAT, and not through NF-kB. In particular, Applicants direct the Examiner's attention to ¶¶ 22 and

et al. in the Discussion section where Holschermann et al. explain that "the marked activation of the NF-*K*B transcription factor . . . was prevented in the presence of high CsA blood concentration." (Emphasis added, Holschermann 1997 at 4237, second full paragraph). Because the pending claims require reducing expression of a gene which has been induced, Holschermann et al. is not evidence of inherent anticipation of the pending claims.

On page 8 of the June 26, 2008 Final Office Action, the Examiner asserted that Figures 3 and 4 show that NF-kB "**correlates with**" TF mRNA expression (emphasis original). In this regard, Applicants note that, as discussed *infra* in footnote 1, Holschermann et al. fails to establish conclusively that CsA acts through NF-*K*B instead of NFAT. Applicants further note that none of the other cited references provide any such evidence. In fact, several studies (see, for example, Giffin 2003 and Kinoshita et al. 1997, both are of record in the subject application) have demonstrated that the consensus sequence used by Holschermann et al. in the EMSA assay to assess NF-*K*B activation (Figure 4) also binds to NFAT. Therefore, the alleged NF-*K*B activation observed in Figure 4 of Holschermann et al. could be the result of NFAT activation. Lacking further verification data, such as control experiments with NF-*K*B specific antibody, there is no evidence to conclude that the binding complex observed in Figure 4 was in fact NF-*K*B. (Declaration of Dr. Verma, ¶73).

In conclusion, because the extrinsic evidence provided by Holschermann et al. does not explain what necessarily occurred in cited prior art, the rejection of the pending claims based on inherent anticipation is improper and should be withdrawn.

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67 of the Declaration of Dr. Verma, where Dr. Verma explains the basis for concluding that the effects of CsA are mediated through NFAT. Thus, Applicants also respectfully submit that the Examiner's assertion that "it is **art recognized** that CsA does inherently affect NF-kB activity" is erroneous (emphasis original).

In fact, Holschermann et al. only confirms that CsA may prevent TF expression, and NF-κB activation to the extent the correlation is valid, but does not show that CsA reduces induced activity. As discussed in the next section, this result is consistent with other studies that have shown CsA cannot reduce induced NF-κB activity.

C. Additional Evidence Showing CsA Cannot Reduce NF-κB Activity When Administered Post NF-κB Induction

Regardless of whether the Examiner's interpretation of the cited references is correct, and the applicants maintain that such an interpretation is erroneous, the 1985 PDR, Griffith et al. I, Griffith et al. II and Holschermann et al. do not and cannot show reduction of induced NF-κB activity.

In addition to the previous discussion in connection with Holschermann et al., other scientific evidence also shows that CsA cannot reduce induced NF-κB activity. Applicants respectfully direct the Examiner's attention to the Second Declaration of Dr. Inder Verma, submitted in connection with the copending reexamination of U.S. Patent No. 6,410,516, to which the subject application is a continuation of. For the convenience of the Examiner, a copy of the Second Declaration of Dr. Inder Verma is attached hereto as **Exhibit C**.

In the Second Declaration, Dr. Verma explained the basis for concluding that CsA is not capable of reducing NF-κB activity, when the administration of CsA is initiated post NF-κB induction. Such evidence is provided by Schmidt et al., J. Virology 64 (8/90):4037-4041; Kronke et al., PNAS 81(1984):5214-5218; and Reed et al., J. Immunol. 137(1986):150-154. These three references were previously cited in the copending reexamination and are of record in the subject application. For the convenience of the Examiner, these references are attached hereto as **Exhibit D-F**, respectively.

As discussed by Dr. Verma in paragraph 12 of the Second Declaration, Schmidt et al. teaches that "direct addition of CsA to a prepared nuclear extract from activated cell had no effect on the factor binding, including binding κB-binding factors (data not shown), which suggests that inhibition occurs during the activation phase of NFAT-1 or the κB complex" (emphasis added, page 4038, second column, second paragraph. Therefore, the Schmidt reference clearly reveals that CsA, when added to activated cells, does not reduce induced NF-κB activity.

Supporting the notion that CsA is not capable of reducing NF-κB activity post induction, Kronke et al. disclosed that "when added 4 hr after induction, CsA did not alter TCGF mRNA levels" (emphasis added, page 5216, second column, second paragraph). TCGF is also known as IL-2, a substance whose expression is affected by CsA as disclosed by the 1985 PDR. Therefore, the Kronke reference plainly shows that CsA is not capable of reducing expression in a human cell of a gene, the expression of which has been induced by an external influence that activated NF-κB.

Further, Reed et al. disclosed that "previous studies by us and by others have demonstrated that CsA (1 to 5 ug/ml) does not interfere directly with IL 2 receptor function in that CsA fails to suppress IL 2-induced proliferation in long-term cultures of activated T-cells" (emphasis added, page 153, second column, first paragraph). As discussed in the previous paragraph, IL-2 expression is affected by NF-κB activity. Therefore, Reed et al., in agreement with Schmidt et al. and Kronke et al., shows that when CsA is administered to cells where NF-κB activity has been previously induced, CsA failed to reduce the expression of a gene where such expression was the result of the induced NF-κB activity.

Therefore, because CsA cannot reduce induced NF-κB activity when used post induction, assuming *arguendo* that CsA does act through NF-κB, any immunosuppressive effect of CsA disclosed in the cited reference could only be explained by prevention of NF-κB induction, not by reduction of induced NF-κB activity.[2]

In conclusion, because the pending claims all recite reducing induced NF-κB activity, the cited CsA references cannot anticipate the pending claims.

[2] Applicants respectfully submit that it is unclear whether CsA affects NF-kB or NFAT.

Response to Double Patenting Rejections

In the June 26, 2008 Final Office Action, the Examiner asserted that "claims 90-91 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-17, 20-63, 88-176 and 192-203 of U.S. Patent No. 6,410,516."

In response, applicant will file a Terminal Disclaimer upon indication of allowable subject matter.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, Applicants direct the Examiner's attention to the following disclosures, which are also listed on the attached substitute Form PTO-1449 (**Exhibit G**).

The subject application is a continuation under 35 U.S.C. §120 of U.S. Application No. 08/464,364, filed June 5, 1995, now U.S. Patent No. 6,410,516, issued June 25, 2002, now undergoing reexamination under Control No. 90/007,503 and 90/007,828 which have been previously disclosed and brought to the Examiner's attention in the subject application.

Applicants note that items 1-2 listed herein were previously submitted to the U.S. Patent and Trademark Office and are readily available to the Examiner and to the public from the file history of U.S. Patent No. 6,410,516 and its merged reexamination proceeding (*Ex Parte* Reexamination Control Nos. 90/007,503, filed April 4, 2005, and 90/007,828, filed December 2, 2005). Accordingly, copies of items 1-2 are not enclosed.

The Examiner is respectfully requested to make the items of record in the subject application by initialing and dating the attached substitute Form PTO-1449, and returning a copy of the initialed and dated form to Applicants' undersigned attorneys.

1. Declaration of Dr. Inder Verma;

2. Second Declaration of Dr. Inder Verma;

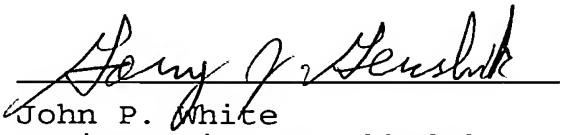
Item 1 was previously disclosed as Exhibit 1 in RESPONSE TO AUGUST 2, 2006 OFFICE ACTION, SUMMARY OF OCTOBER 13, 2006 EXAMINER INTERVIEW, STATEMENT OF CONCURRENT PROCEEDINGS UNDER 37 C.F.R. §1.565, AND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT, filed December 9, 2006, in connection with merged *Ex Parte* Reexamination Control Nos. 90/007,503 and 90/007,828.

Item 2 was previously disclosed as Exhibit B in RESPONSE TO JULY 6, 2007 FINAL OFFICE ACTION, SUMMARY OF AUGUST 22, 2007 EXAMINER INTERVIEW, STATEMENT OF CONCURRENT PROCEEDINGS UNDER 37 C.F.R. §1.565, AND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT, filed October 22, 2007, in connection with merged *Ex Parte* Reexamination Control Nos. 90/007,503 and 90/007,828.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed fee of $1,110.00 for three-month extension of time, is deemed necessary in connection with the filing of this Response. However, if any other fee is required, authorization is hereby given to charge the additional amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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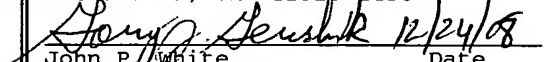

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